REMARKS

I. REQUEST FOR WITHDRAWAL OF REJECTIONS AND PROMPT ISSUANCE OF NOTICE OF ALLOWANCE

Reconsideration and withdrawal of the rejections of the present application and prompt issuance of a Notice of Allowance are respectfully requested in view of the amendments, remarks, and accompanying and/or attached documents, including Declarations, herewith.

II. REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, prior to issuance of any paper (other than a Notice of Allowance), an interview, with supervisory review, is respectfully requested, especially in view of the amendments, remarks, and accompanying and/or attached documents, including Declarations, herewith; and, pursuant to this request, **the undersigned, or a colleague on his behalf, shall be calling** the Examiner and his SPE, Christina Chan, **on or about Monday, June 17, 2002, to schedule a mutually convenient time and manner for the interview or to learn that an interview is unnecessary** in view of the amendments, remarks, and accompanying and/or attached documents, including Declarations, herewith.

III. THE PATENTABLE CLAIMS

Presented herewith are claims 56-79. It is submitted that the claims previously pending and the claims presented herewith are patentably distinct from the prior art cited by the Examiner, and that these claims are in full compliance with the requirements of 35 U.S.C. §112. The presentation herewith of claims is not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather claims are presented simply for clarification and to round out the scope of protection to which Applicants are entitled. Indeed, it is also noted that claims 56-79 are not considered narrower than previously presented claims; and hence, claims 56-79 are presented without prejudice, without admission, without surrender of subject matter and without any intention of creating any estoppel as to equivalents. Support for claims 56-79 can be found throughout the present application. Thus, no new matter is added.

More specifically, claims 56-79 provide methods for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein; and, each of the claims specifies that the self- protein is autotolerated by the animal and that there is normally B-cell autotolerance by the

animal to the self-protein, as well as whereby, the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

That the instant invention involves such methods, and especially methods for breaking B-cell autotolerance to a self-protein wherein the self protein is autotolerated and there is normally B-cell sutotolerance to the self-protein, is supported by, *inter alia*, the disclosure at pages 1, 2-3, 4-6 and 9-11, and the Examples and Figures and the discussion thereof throughout the application; including disclosure at pages 5 and 10 (where there is disclosure of "breaking the B-cell autotolerance"), pages 2-3 (where there is a disclosure that T-cell epitopes are inserted into the self-protein for the purpose of raising antibodies and that "[t]he tolerance towards the self protein is broken"), pages 4-6 (breaking autotolerance), page 1 (discussion of the immune system and that B-cells produce antibodies and defining self-protein as proteins "individuals generally do not harbour autoantibodies in their serum ... to") and the original claims.

All of the claims provide that the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein. Claims 57 and 63-67, 69, 70, 71, and 72 recite that the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein. The disclosure at pages 2-3, 6, 9, and 10 and in the original claims and Abstract and in the original Examples and Figures and the discussion thereof throughout the application, *inter alia*, provides for substitution of at least one fragment of the self-protein with a foreign immunodominant T-cell epitope and preserving tertiary or secondary and tertiary structure of the self-protein or minimally changing the tertiary structure or minimally obscure the tertiary structure.

Claim 58 provides that the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment, whereas claim 59 calls for flanking regions comprising at least ten amino acids on each side of

the peptide fragment, and, claim 60 recites flanking regions comprising at least fifteen amino acids on each side of the peptide fragment. Claims 63-65 call for the flanking regions and preserving secondary and tertiary structure. And flanking regions are also mentioned in claims 70, 71 and 72. In addition to the foregoing and herein citations presented for support, the disclosure throughout the application, including the original claims and the Examples and Figures and the disclosure thereof throughout the application, supports flanking regions.

Claim 61 provides that "the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken." Claim 66 recites that "the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken." Such recitations also appear in claims 70, 71 and 72. Support for these recitations may be found throughout the application, including pages 1, 6, 9-10, and the Examples and Figures and the description thereof in the application, as well as the previously provided citations for support.

Claim 62 provides that the modified self-protein is modified, in comparison to the self-protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein; and, claim 67 recites that the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein

with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, with the substitution preserving secondary and tertiary structure of the self-protein. Such recitations are also found in claims 70, 71 and 72. In addition to the foregoing and herein citations provided for support, these recitations are supported throughout the entire application, including at page 9 and the Examples and Figures and the description thereof throughout the application.

Claim 68 recites a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

And, claim 69 provides a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

These claims are supported by the disclosure throughout the application, the text at page 9 of the application, the Examples and Figures including the description thereof throughout the application, particularly Example 6 at pages 15-16 and the description thereof in the application.

Claims 70, 71 and 72 recite as subparts a. to n. recitations of claims 56-69 in the alternative. Claim 70 calls for a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein. Claim 71 provides a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, inducing antibody production in the animal against the self-protein of that animal, and eliciting an immune response in the animal which includes an MHC class II immune response as to an immunodominant T-cell epitope which is foreign to the animal and an autoantibody response in other MHC-haplotypes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein. And claim 72 provides a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-

protein, and specifies that the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein. These claims are supported by the foregoing citations, and throughout the instant application, including, the original claims and the Examples and Figures and the disclosure thereof throughout the application, including pages 6 ("MHC class II immune response as to an immunodominant T-cell epitope which is foreign to the animal and an autoantibody response in other MHC-haplotypes"), 9 ("stronger autoantibody response ... *not* restricted to the MHC molecules of the immunized mouse"), and 10 ("induce antibodies in a broad population of MHC molecules") and Examples 2, 3 and 4 (response not restricted to the MHC molecules of the immunized mice), Example 4 and Figure5 and the description thereof in the throughout the application (higher and titres in comparision to the self-protein conjugated to carrier protein or polypeptide containing T-cell epitopes); and page 1 ("individuals generally do not harbour autoantibodies in their serum ... to ... the individual's own proteins (the so-called self-or autoproteins)" hence self-proteins are "normally non-immunogenic"), *inter alia*.

Claim 73 calls for a method of claims 56-72 wherein the modified self-protein is a recombinant modified self-protein. Claims 74 and 75 provide methods of claims 56-73 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE). Claims 76, 78, 79 involves the method of claims 56-73 and 75 wherein the administering includes administering an adjuvant, with claim 77 reciting that the adjuvant comprises calcium phosphate, saponin, quil A or a biodegradable polymer. These claims are supported by the foregoing citations, and throughout the instant application, including, the original claims and the Examples and Figures and the disclosure thereof throughout the application, including pages 6, 7, 9, 10, 11, 12, 13, 14, 16, 19.

Thus, it is clear that no new matter is added; and, it is also mentioned that recitation of the claims parallel recitations in previously pending claims, such that claims 56-79 are not considered narrower than previously presented claims; hence, claims 56-79 are presented without prejudice, without admission, without surrender of subject matter and without any intention of creating any estoppel as to equivalents.

IV. ALL THE REJECTIONS, INCLUDING UNDER SECTIONS 112, 102 & 103 ARE OVERCOME, INCLUDING THROUGH EXPERT DECLARATIONS OF A NOBEL PRIZE LAUREATE AND A PRE-EMINENT TEXTBOOK AUTHOR, AND ATTACHMENTS REBUTTING THE EXAMINER, AND DECLARATIONS OF COMMERCIAL, FINANCIAL AND TECHNICAL SUCCESS OF THE INVENTION

A. *Rejections and/or objections of the November 27, 2001 Office Action are prima facie clearly erroneous and are addressed collectively*

The November 27, Office Action contains a rejection of claims 54 and 55 under Section 112, first paragraph as allegedly containing subject matter not described in the specification. Claims 26, 28, 45-47 and 53-55 were rejected under Section 112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the invention. It is noted that the Office Action seems to not have considered the October 6, 2000 Declaration of Dr. Paul J. Travers, as well the disclosure in the present application on these issues. It is respectfully submitted that these failures make the rejections clearly erroneous.

The Office Action rejects claims 26, 28, 45, 46, 54 and 55 were rejected under Section 102(b) as allegedly anticipated by Russell-Jones, WO92/05192, with citations to Russell-Jones and two Abstracts, Miller et al., J. Immunology 151(12):7307-7315 (1993) and Parkar et al., J. Immunol Methods 120(2):159-166 (1989).

In particular, Example 5 of Russell-Jones is cited in the Office Action. This Example, as characterized by the USPTO in the prosecution of USSN 08/614,626,[1] "merely provide[s] a proposal that the removal of suppressor regions HIV external epitope protein [gp120 – a major surface antigen of HIV]." Hence, the Example provides only a hypothesis that one can replace "suppressor regions" in gp120. Contrary to accepted practice that a lack of novelty Section 102 rejection rely upon a single document, in the Section 102(b) rejection based on Russell-Jones, the Office Action also cites two Abstracts, Miller et al., J. Immunology 151(12):7307-7315 (1993) and Parkar et al., J. Immunol Methods 120(2):159-166 (1989), for the assertion that there are suppressor epitopes in mammalian proteins, as well as for the incredible proposition that Dr. Paul

[1] From which issued U.S. Patent No. 5,928,644, corresponding to Russell Jones; *see* Exhibit A: copy of said U.S. Patent and pages 1-3 of paper No. 6 from prosecution thereof.

Travers, an internationally acknowledged and recognized immunologist, is somehow "not an expert in the particular technology relevant to the claimed invention."

It is respectfully submitted that the use of three documents in a Section 102(b) rejection, makes the Section 102(b) rejection clearly erroneous.[2] The incredible proposition in the Section 102(b) rejection that Dr. Travers is not an expert makes the Section 102(b) rejection clearly erroneous, especially considering the education, training and experience of Dr. Travers, including "Immunobiology - The Immune System In Health and Disease," by Charles Janeway, Jr. and Paul Travers. Garland Publishing, Inc., now in its Fifth edition (2001) - "the preeminent textbook Janeway/Travers Immunology"; "probably the most widely known and recognized textbook in immunology in the world." And the failure to fully and/or fairly consider Dr. Travers' October 6, 2000 Declaration, with respect to Dr. Travers as either or both an expert and a man of ordinary skill in the art in view of his education, training and experience, especially in view of the standard being the "person having ordinary skill in the art to which [the] subject matter [sought to be patented] pertains," it is respectfully submitted, makes the Section 102(b) rejection clearly erroneous.

Then, the Office Action seems to provide an indefinite number of vague rejections under Section 103 with an allegation of unpatentability of claims 26, 28, 45-47, and 53-55 "over Russell-Jones ... in view of Hellman (WO 93/05810), Etlinger **and prior art disclosed in the specification (page 18, last paragraph)**" (emphasis added), making the rejection *prima facie* clearly erroneous.[3]

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[2] It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.*, 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). Hence, the Section 102(b) is *prima facie* clearly erroneous. It is also noted that the use of Abstracts in a rejection can be a basis for Board reversal of a rejection. *See Ex parte Jones*, 62 USPQ2d 1206 (Bd PatApp&Int. 2001) (copy supplied for convenience in Exhibit B; and, while not precedent, is indicative of a Board's view of the citation of Abstracts).

[3] There are no less than four articles cited in the last paragraph of page 18 of the specification: F.M. Brennan et al. Br. J. Rheumatol. 31, 293-298, 1992; M. Odeh, J. Intern. Med. 228, 549-556, 1990; B.P. Giroir, Crit. Care. Med., 21, 780-789, 1993; CH Lang et al., Endocrinology, 130, 43-52, 1992. It is likewise unclear whether the Examiner relies upon each of these four documents individually with Russell-Jones and Hellman and Etlinger – a minimum number of four rejections; or, whether the Examiner also relies upon combinations of these four documents, leading to an indefinite number of rejections. It is likewise unclear where within the cited documents the rejections are allegedly supported, thereby making the rejections vague. Hence, the rejections are *prima facie* clearly erroneous and should be reconsidered and withdrawn. See *Ex parte Gambogi*, 62 USPQ2d 1209 (Bd PatApp&Int. 2001) (copy supplied for convenience in Exhibit B; and, while not precedent, is indicative of a Board's view on multiple rejections ("no less than 36 separate

Each and all rejections of the claims, and any objections to the application and/or claims, of the November 27, 2001 Office Action, including the foregoing, and the patentability of the present claims, is addressed collectively herein.

And, it is respectfully requested that the rejections of the claims, and any objections to the application and claims of the November 27, 2001 Office Action, be reconsidered and withdrawn having been improperly made and hence as being clearly erroneous.[4]

In short, the Section 112 rejections should be reconsidered and withdrawn because the Examiner, in making these rejections, failed to fully and fairly consider Dr. Travers' First Declaration, which addresses these issue; and, on this basis, reconsideration and withdrawal of the Section 112 rejections are respectfully requested. The Section 102 rejection should be reconsidered and withdrawn because it involves more than one document, and is based upon an improper dismissal of Dr. Travers' First Declaration and the erroneous assertion that Dr. Travers is not an expert in the field to which the invention pertains; and, on these bases, reconsideration and withdrawal of the Section 102 rejection are respectfully requested. The Section 103 rejection should be reconsidered and withdrawn because it is impermissibly vague and indefinite by not pointing out specifically which documents are involved in the rejection and where in the documents the Examiner finds support for the rejection, and also because it too is based upon an improper dismissal of Dr. Travers' First Declaration and the erroneous assertion that Dr. Travers is not an expert in the field to which the invention pertains; and, on these bases, reconsideration and withdrawal of the Section 103 rejection are respectfully requested.

B. ***Introduction of the herewith Declarations which clearly and convincingly demonstrate the patentability of the instant invention***

In addition to the remarks herewith and other attachments or Exhibits supplied herewith, submitted herewith is: the Declarations of ROLF M. ZINKERNAGEL, PhD (Exhibit C) (Zinkernagel Declaration), JAKOB SCHMIDT, M.Sc. (Exhibit E) (Schmidt Declaration), and

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rejections") and vague rejections, e.g., rejections made without specifying where in each reference the Examiner is relying for basis for the rejection).

[4] Also, it is noted that any second or subsequent Office Action cannot be made final because it cannot be said that this paper has necessitated any further or subsequent rejection or objection because rejections of the November 27, 2001 Office Action were so clearly erroneous and indefinite and vague: Any further search, examination, or objection or rejection is necessitated by rejections of the November 27, 2001 Office Action having been clearly erroneous and indefinite and vague.

BIRGER BORREGAARD, M.Sc., MBA (Exhibit F) (Borregaard Declaration), as well as a SECOND DECLARATION of PAUL J. TRAVERS, PhD (Exhibit D). Dr. Zinkernagel supports the position that Dr. Travers is an expert in the field to which the present invention pertains and concurs with opinions presented by Dr. Travers, demonstrating that the positions taken in the Office Action cannot be maintained. Dr. Travers rebuts the positions taken in the Office Action, with respect to both his credentials and the teachings in the art, demonstrating that the positions taken in the Office Action are untenable. Messrs. Schmidt and Borregaard demonstrate the technical, commercial and financial success of the instant invention.

Dr. Zinkernagel is familiar with the subject matter of the above-captioned application (the present application) as: he is informed that a concurrently-filed Amendment (this paper) presents claims as herein which he read and understood; he has been informed that the Examiner has indicated that Dr. Paul Travers - a previous declarant in the present application - is not a person knowledgeable in the field of immunology or more specifically in the field relating to immunosuppression; and he has been informed that the Examiner, in rejecting claims, has indicated that it would have been obvious for an immunologist to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes or that an immunologist could have substituted suppressor epitopes in self proteins with T-helper epitopes. Dr. Zinkernagel's *Curriculum vitae* is publicly available at *inter alia* http://www.nobel.se/medicine/laureates/1996/zinkernagel-cv.html, is attached to his Declaration and incorporated therein by reference. Among other accomplishments, he was awarded the Nobel Prize in Physiology or Medicine with Peter C. Doherty, PhD, in 1996, for their discoveries concerning the specificity of the cell mediated immune defense. Accordingly, he is well qualified to speak as to the present application and Dr. Travers' qualifications.

Paul J. Travers, PhD – the declarant in the herewith Second Declaration of Paul J. Travers, PhD - executed a Declaration dated October 6, 2000 (his First Declaration), which is incorporated by reference into his herewith Declaration, including the *Curriculum vitae* attached thereto. He advises that "Immunobiology - The Immune System In Health and Disease," by Charles Janeway, Jr. and Paul Travers. Garland Publishing, Inc. is now in its Fifth edition (2001) (also known as the "Janeway/Travers Immunology" textbook). Indeed, he is advised that some have called Immunobiology - The Immune System In Health and Disease," "the preeminent textbook Janeway/Travers Immunology" and characterized it as "probably the most widely

known and recognized textbook in immunology in the world." Furthermore, in addition to having read and understood the disclosure in the present application, as discussed in his First Declaration, he is informed that a concurrently-filed Amendment (this paper) presents claims as herein presented, which he has read and understood. Accordingly, in view of his education, training and experience, Dr. Travers is well qualified to speak as to the present application and the state of the art to which it pertains, contrary to any different assertions by the Examiner.

More specifically, Dr. Travers is informed that in the November 27, 2001 Office Action, the Examiner has asserted that he is not a person knowledgeable in the field of immunology or more specifically in the field relating to immunosuppression; and has been informed that the Examiner, in rejecting claims, has indicated that it would have been obvious for an immunologist to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes or that an immunologist could have substituted suppressor epitopes in self proteins with T-helper epitopes. The Second Declaration of Paul J. Travers, PhD is directly responsive to these points and the November 27, 2001 Office Action. Hence, the October 6, 2000 Declaration of Dr. Travers, the herewith Second Declaration of Paul J. Travers, PhD, and the herewith Zinkernagel Declaration, rebut the Examiner and the positions set forth in the November 27, 2001 Office Action; and, demonstrate the patentability of the present invention.

Jakob Schmidt is the Chief Financial Officer of Pharmexa A/S (Pharmexa), and has held this position since about February 2000. Prior to being the CFO of Pharmexa, he was a Project Manager with Carnegie Bank Corporate Finance for 6 years, responsible for Carnegie's Healthcare and Equity Capital Market activities in Denmark. He has managed a number of initial public offerings (IPOs) and private placements in biotechnology companies and other high growth companies in recent years. Prior to joining Carnegie, he undertook Ph.D. studies at the Institute of Finance, Copenhagen Business School, focusing on the financial problems of start up, high growth companies and teaching a number of graduate and undergraduate courses on high technology and start-up financing at Copenhagen Business School. He has also studied medicine at Aarhus University and international economics and finance at Brandeis University, Boston. He is also a member of the Board of Directors of Inoxell A/S, and of the Danish Investor Relation Society (DIRF). He is responsible for Pharmexa's financial activities, and is authorized to speak on behalf of Pharmexa. Pharmexa is the assignee of the above-captioned application (the present application), by virtue of assignment from the inventors and a corporate

name change (from M&E Biotech). From his education, training and experience, including his experience, including his experience at Pharmexa, he is familiar with the subject matter of the present application, including that he is informed that a concurrently-filed Amendment (this paper) presents claims as herein presented, which he has read and understood. Accordingly, Jakob Schmidt is well qualified to speak as to the present application, and particularly, success of the present invention, such as the commercial or financial success of the present invention, including financing generated - indicia of patentability – and hence, the Schmidt Declaration demonstrates the patentability of the present invention.

Birger Borregaard is the Chief Operating Officer of Pharmexa A/S (Pharmexa), and has held this position since about February 2000. Prior to being the COO of Pharmexa, he was the Director of Business Development with Pharmexa, a position he held from mid-1998, when he joined Pharmexa, to about February 2000, when he was promoted to COO of Pharmexa. In his position of COO of Pharmexa, he remains responsible for Pharmexa's business development activities, and is authorized to speak on behalf of Pharmexa. He holds an M.Sc. in biology from University of Copenhagen and a Henley MBA. Prior to joining Pharmexa, he served as CEO of Dansk Biologisk Production AMBA, as Executive Assistant to the CSO at the State Serum Institute, Copenhagen, and has held various positions with Novo Nordisk A/S, including Business Development Manager. He serves as a member of the board of the commercial trust Henley MBA in Denmark and is a former chairman of the Henley Alumni Association - Denmark. From his education, training and experience, including his experience at Pharmexa, he is familiar with the subject matter of the present application, including that he is informed that a concurrently-filed Amendment (this paper) presents claims as herein presented, which he has read and understood. Accordingly, Birger Borregaard is well qualified to speak as to the present application, and particularly, success of the present invention, such as the commercial success of the present invention, including licenses that have been granted and financing generated, and technical or art-recognized success, including trials and publications - indicia of patentability – and hence, the Declaration of Birger Borregaard demonstrates the patentability of the present invention.

As to the Borregaard and Schmidt Declarations, at Pharmexa, they proudly refer to the present invention as AutoVac™ technology; and, this term shall also be used herein.

It is respectfully requested that the Declarations submitted herewith be fully considered and that the October 6, 2000 Declaration of Dr. Paul J. Travers be fully considered, and that the other attachments and remarks herewith also be fully considered; and, that in view of the amendments, remarks, attachments, Exhibits, and Declarations herewith and the remarks and, documents previously submitted, including the October 6, 2000 Declaration of Dr. Paul J. Travers, that the objections to and rejections of the present application be reconsidered and withdrawn.

C. *Dr. Paul J. Travers is indeed an expert - "no one in the field of immunology would or could reasonably concur with the Examiner's opinion" – and the rejections based on Russell-Jones must fail*

1. Dr. Travers is indeed an expert

As an initial matter, an October 6, 2000 Declaration of Dr. Paul J. Travers was previously submitted and the Office Action, in making the Section 102(b) rejection based on Russell-Jones, incredibly dismisses the October 6, 2000 Travers Declaration (or First Travers Declaration), asserting at page 6 "that Travers is not an expert in the particular technology relevant to the claimed invention."

It is respectfully submitted that bases for the Section 102(b) rejection based on Russell-Jones (and hence also the indefinite and vague Section 103 rejection based on Russell-Jones in view of Hellman, Etlinger "and prior art disclosed in the specification ..."), include, *inter alia*, the Examiner's dismissal of the October 6, 2000 Travers Declaration, the Examiner's allegations of equivalence between "suppressor regions" of the immunogen gp120 and hypothetical "suppressor epitopes" of mammalian proteins and that one could substitute foreign T-cell epitopes for these hypothetical "suppressor epitopes" based on the proposal[5] to substitute "suppressor regions" of immunogen gp120 in Russell-Jones Example 5 and reliance on the Parkar and Miller Abstracts[6], and, the Examiner's overly broad reading of Russell-Jones, including Russell-Jones' Example 5 and text at pages 8-9 of Russell-Jones, and especially to the

[5] *See* Exhibit A: copy of U.S. Patent No. 5,928,644, corresponding to Russell Jones and pages 1-3 of paper No. 6 from prosecution thereof, where the USPTO characterized Example 5 of Russell-Jones as merely a proposal; *see also* footnote 1, *supra*, and main text therefor.

[6] *See supra* footnote 2 and the accompanying main text for the discussion as to why reliance on more than one document for a Section 102(b) rejection is *prima facie* improper, and how a Board may react to citations of

point of "strain[ing] the term 'immunogen' well beyond its well-known, ordinary, art-accepted definition" (Second Travers Declaration).[7]

In response to the dismissal of the First Travers Declaration, and, of course, also as to the rejections based on Russell-Jones and more generally all rejections of the November 27, 2001 Office Action,[8] not only is a Second Declaration of Dr. Paul J. Travers submitted herewith (Exhibit D), but also, a Declaration of Dr. Rolf. M. Zinkernagel (Exhibit C) in support of Dr. Travers and Dr. Travers' positions. Dr. Zinkernagel is a Nobel Prize Laureate: among other accomplishments, Dr. Zinkernagel was awarded the Nobel Prize in Physiology or Medicine with Peter C. Doherty, PhD, in 1996, for their discoveries concerning the specificity of the cell mediated immune defense. Furthermore, in addition to his attached *Curriculum vitae*, in paragraph 1 of his Declaration, Dr. Zinkernagel shows that he is well qualified to speak as to the present application and Dr. Travers' qualifications.

More in particular, in paragraphs 2-4 of his Declaration, Dr. Zinkernagel confirms that Dr. Travers is well known as being quite knowledgeable in the field of immunology and in the field of immunosuppression and respectfully disagrees with the Examiner's opinion of Dr. Paul Travers.

Abstracts, demonstrating that the Section 102(b) rejection is clearly erroneous and warrants reconsideration and withdrawal.

[7] As well as other views, which, it is respectfully submitted, do not seem to make sense in the context of the present invention, such as alleging - without any data - that there is in Russell-Jones, "insert[ion] into the immunogen in such a manner as to 'essentially preserve the overall tertiary structure' or 'to introduce minimal tertiary structure changes' or 'to essentially preserve a maximum number of B-cell epitopes', because the ability of the immunogen to function as an immunogen is maintained" (*Office Action*, at 6). The instant invention involves self-proteins which are non-immunogenic or B-cell autotolerated. If the function of the self-proteins is maintained after substitution of a portion thereof with a foreign T-cell epitope, then the resultant modified self-protein would remain non-immunogenic or B-cell autotolerated as such is the function of the self-protein, and the purpose of the invention would be defeated as the self-proteins. Hence, preserving overall tertiary or secondary and tertiary structure and having an immunogenic modified self-protein as recited in the present claims is novel and non-obvious; following the Examiner's reasoning, one would not necessarily expect the success of the instant invention (*see infra*) by preserving tertiary or secondary and tertiary structure as one would expect that function would be maintained (as such is asserted to be taught be the Examiner in Russell-Jones) and if the function of the self-proteins is maintained then the modified self-proteins would be non-immunogenic or B-cell autotolerated as that is the function of the self-protiens. Accordingly, it is respectfully submitted that the Examiner's reliance in rejecting claims on alleging that function is maintained in Russell-Jones does not make sense.

[8] Including because in reconsidering and withdrawing the Section 112 rejections, it is respectfully submitted that full and fair consideration of the First Travers Declaration is warranted, as such issues are addressed in that Declaration, (*see* paragraphs 4-8 thereof) and the Office Action is silent on the Travers Declaration as to the Section 112 rejections, indicating that the First Travers Declaration was not fully considered as to all of the issues to which it

In the view of Nobel Prize Laureate Dr. Zinkernagel, Dr. Paul Travers is the prominent author of the preeminent textbook Janeway/Travers Immunology. Dr. Zinkernagel states that this textbook is probably the most widely known and recognized textbook in immunology in the world. Hence, Dr. Zinkernagel concludes that Dr. Paul Travers is an internationally acknowledged and recognized immunologist. Dr. Travers, in Dr. Zinkernagel's opinion, has a profound knowledge of the basic functioning of the immune system, especially as reflected by Dr. Travers being the prominent author of the preeminent textbook Janeway/Travers Immunology – again probably the most widely known and recognized textbook in immunology in the entire world.

Accordingly, **Dr. Zinkernagel respectfully submits that no one in the field of immunology would or could reasonably concur with the Examiner's opinion that Dr. Paul Travers is not a person knowledgeable in the field of immunology, or more specifically, in the field relating to immunosuppression; and, he respectfully disagrees with this opinion of Dr. Paul Travers by the Examiner**.

Furthermore, Dr. Zinkernagel confirms or concurs with views of Dr. Travers.

More specifically, Dr. Zinkernagel is also informed that the Examiner has indicated that it would have been obvious for an immunologist to substitute supressor epitopes in self-proteins with foreign T-helper epitopes.

As a person clearly skilled in the field of immunology, and indeed recognized as an expert in the field of immunology, Dr. Zinkernagel respectfully submits, based on his education, training and experience, that the Examiner's hypothetical substitution of suppressor epitopes in self-proteins with foreign T-helper epitopes, is today not possible, and was not possible at the August 26, 1993 effective filing date of the present application; and therefore, that it could not have been obvious for an immunologist to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes.[9]

Simply, Dr. Zinkernagel, as a person clearly skilled in the field of immunology, and indeed recognized as an expert in the field of immunology, based on his education, training and

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speaks and therefore, the response to the dismissal of the First Travers Declaration is a response to all rejections of the Office Action.

[9] And this provides yet another reason why the rejections based on Russell-Jones must fail; *cf.* footnote 2, *supra*, and citations thereat.

experience, fails to see how the Examiner's hypothetical substitution of suppressor epitopes could be possible today or could have been possible at the August 26, 1993 effective filing date of the present application.

Dr. Zinkernagel states that even today, it is highly controversial whether there exists such a thing as supressor epitopes; but, more importantly, there is, to the best of his knowledge, no known method of positively identifying such suppressor epitopes.

Accordingly, Dr. Zinkernagel states that at the August 26, 1993 effective filing date of the present application, to the best of his knowledge, there was no known method of positively identifying such suppressor epitopes, and consequently it is not possible today – and was not possible at the August 26, 1993 effective filing date of the present application - to devise any strategy for substituting supressor epitopes with foreign T-helper epitopes.

Dr. Zinkernagel declares: "Clearly, if one skilled in the art could not and cannot positively identify suppressor epitopes in self-proteins (whose existence is still a matter of debate in the art), based on my education, training and experience, there is no way and was no way for the skilled artisan to perform the hypothetical substitution postulated by the Examiner."

Dr. Zinkernagel further declares: "Thus, it was not obvious and is not obvious for an immunologist to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes, contrary to the Examiner's hypothesis that it would have been obvious to substitute suppressor epitopes in self-proteins with foreign T-helper epitopes, with which, based on my education, training and experience, I respectfully disagree."

Hence, Dr. Zinkernagel is in accord with Dr. Travers' views (*compare* Travers' First Declaration, e.g., paragraphs 10-16; *see also* herewith Second Declaration of Paul J. Travers).

It is respectfully submitted that under the *Daubert* standard, the admissibility of scientific evidence is based on a reliability test, e.g.: Is the scientific evidence proffered reliable? Is the testimony relevant and reliable, including considering the acceptability in the relevant scientific community? *See Daubert v. Merril Dow Pharm. Inc.*, 509 U.S. 579, 593-94 (1993). And that under the *Frye* standard, the admissibility of scientific expert opinion is based on whether the opinion is generally accepted as reliable in the scientific community, e.g.: Is the scientific expert opinion generally accepted in the scientific community? *See U.S. v. Frye*, 293 F. 1013, 1014 (D.C. Cir. 1923).

Under these standards, **clearly Dr. Travers is an expert in the field to which the present invention pertains, and his testimony and opinions are admissible and should be and should have been fully and fairly considered: Dr. Travers has impressive credentials, including being the author of possibly the best known textbook in the field; and, his views are confirmed by a Nobel Prize Laureate in the field – Dr. Zinkernagel. And Dr. Travers' views are accepted in the relevant scientific community**. Furthermore, it is noted that the standard is the person of ordinary skill in the art, and clearly Dr. Travers is at the very least a skilled artisan, and therfore Dr. Travers' FirstDeclaration and all his views therein were entitled to at least that consideration.

Therefore, it is respectfully submitted that the Examiner's dismissal of the First Travers Declaration was clearly erroneous. It is respectfully requested that the First Travers Declaration be fully and fairly considered as Dr. Travers is indeed an expert in the field to which the present invention pertains, e.g., immunology, as well as a person clearly skilled in the field to which the present invention pertains, e.g., immunology. And, in his Second Declaration, Dr Travers also respectfully submits that his credentials amply demonstrate that he is indeed "an expert in the particular technology relevant to the claimed invention," contrary to the Examiner's assertion in the November 27, 2001 Office Action. Accordingly, Dr. Travers respectfully invites the Examiner to reconsider and withdraw his contrary assertions as to Dr. Travers' credentials as set forth in the November 27, 2001 Office Action.

It is respectfully requested that the Examiner reconsider and withdraw his assertions as to Dr. Travers' status in the field, and fully and fairly consider The First Travers Declaration (as well as the herewith Second Travers Declaration and the herewith Zinkernagel Declaration), particularly in view of matters discussed herein and other documents filed concurrently herewith. And Dr. Travers respectfully invites the Examiner to make his credentials of record so that any reviewer of the file of the present application (e.g., Board of Patent Appeals & Interferences) may compare and contrast his credentials with Dr. Travers, and those of any other declarants (e.g., Dr. Zinkernagel, Nobel Prize Laureate), so that the reviewer can judge for himself or herself who is best qualified to address the present invention and the field to which it pertains.

2. Drs. Travers and Zinkernagel, in their Declarations, clearly and convincingly rebut the Examiner – the rejections based on Russell-Jones must fail

As discussed above, claims 26, 28, 45, 46, 54 and 55 were rejected under Section 102(b) as allegedly anticipated by Russell-Jones, WO92/05192, with citations to Russell-Jones and two Abstracts, Miller et al., J. Immunology 151(12):7307-7315 (1993) and Parkar et al., J. Immunol Methods 120(2):159-166 (1989) and, the Office Action thereafter provides an indefinite number of vague rejections under Section 103 with an allegation of unpatentability of claims 26, 28, 45-47, and 53-55 "over Russell-Jones ... in view of Hellman (WO 93/05810), Etlinger **and prior art disclosed in the specification (page 18, last paragraph)**" (emphasis added).

These rejections, it is respectfully submitted, are based in the Examiner's assertions at pages 6-11 of the Office Action which are essentially that the Examiner has cited Example 5 of Russell-Jones, WO 92/05192, which involves HIV gp120 – a major surface antigen of HIV – and the hypothesis that one can replace "suppressor regions" therein. From this, it is respectfully submitted that, the Examiner cites Miller and Parkar for the assertion that there are suppressor epitopes in mammalian proteins, and relies on these Abstracts to assert that "mammalian proteins containing suppressor regions/epitopes are well known in the art" and to attempt to discredit Dr. Travers as an expert. Thus the Examiner has equated the "suppressor regions" of gp120 with postulated, hypothetical "suppressor epitopes" in the Abstracts to assert that the instant invention is disclosed by or obvious from Russell-Jones.

The Examiner's positions are clearly rebutted in the Declarations of Drs. Zinkernagel and Travers.

Dr. Zinkernagel's Declaration is summarized herein, e.g., above. Dr. Travers' First Declaration has been discussed previously in the prosecution. The Examiner is respectfully invited to review the herein summary of Dr. Zinkernagel's Declaration, as well as papers previously in the prosecution, including Dr. Travers' First Declaration.

Dr. Travers, in his herewith Second Declaration, expands upon his First Declaration, and demonstrates that the Examiner's position is contrary to the art and cannot result in the instant invention. And note how Dr. Zinkernagel concurs with Dr. Travers.

More in particular, Dr. Travers, in his Second Declaration, e.g., paragraphs 5 and 6, summarizes his familiarity with the bases for the rejections based on Russell-Jones.

In paragraph 7 of his Second Declaration, Dr. Travers explains that a full reading of Miller et al. shows that the same epitope can be either activating or suppressive depending on the route and nature of administration and that in general to speak of a "suppressive epitope" in isolation of these other factors is inappropriate; in paragraphs 8 and 9, Dr. Travers rebuts the Examiner's assertions in the Office Action; and, it is again noted that Dr. Travers' views are confirmed by Dr. Zinkernagel (*see* discussion above).

Dr. Travers' reading of the Examiner's comments is that the Examiner refers to epitopes which are intrinsically or constitutively suppressive. In Dr. Travers' opinion, as confirmed by Dr. Zinkernagel (*see* discussion above), it is highly controversial whether such suppressor epitopes exist; but, more importantly, there is, to the best of Dr. Travers' knowledge, no known method of positively identifying such suppressor epitopes. And at the August 26, 1993 effective filing date of the present application, to the best of Dr. Travers' knowledge, there was no known method of positively identifying such suppressor epitopes. Again, these views are confirmed by Dr. Zinkernagel.

Indeed, Dr. Travers notes that Parkar, for example, is seeking to "facilitate the mapping of ... suppressor epitopes" indicating that there was no known method for positively identifying such suppressor epitopes.

Dr. Travers notes further Etlinger, "Carrier sequence selection – one key to successful vaccines," Immunology Today, Vol. 13 No. 2 pp 52-55 (copy attached to his Second Declaration) which also shows that there were no methods available for the identification of T-suppressor epitopes (*cf.* Etlinger at p 53, right-hand column, first full paragraph).

Simply, both Dr. Travers and Dr. Zinkernagel confirm that it is not possible today - and was not possible at the August 26, 1993 effective filing date of the present application - to devise any strategy for immunization by substituting suppressor epitopes of self-proteins with foreign T-helper epitopes.

Clearly, if one skilled in the art could not and cannot positively identify suppressor epitopes in self-proteins (whose existence is still a matter of debate in the art), based on Dr. Travers' education, training and experience, there is no way and was no way for the skilled artisan to perform the hypothetical substitution postulated by the Examiner.

Accordingly, Russell-Jones cannot teach or suggest the instant invention as Russell-Jones does not teach, suggest and enable the instant invention (*see* footnote 2 and main text therefor

and the cases cited therein: For a Section 102 rejection, the prior art must enable the claimed invention; and, Drs. Travers and Zinkernagel confirm that Russell-Jones does not enable the instant invention).

Moreover, Dr. Travers states that if "suppressor epitopes" do exist, a suppressor epitope would activate suppressor T-Lymphocytes, whereas the "suppressor region" of gp120 is implicated in leading to a depletion of CD4+ cells (loss of T-helper cells and/or function).

Hence, even if "suppressor epitopes" do exist, they are different than the gp120 suppressor region; and, their function would be totally different than that of the gp120 "suppressor region".

Russell-Jones demonstrates that the suppressor peptide of gp120 provides for a general lack of immune responsiveness, i.e., an antigen unspecific suppression.

In contrast, if such a thing as a specific T-suppressor epitope would exist, it would by nature provide for an antigen specific response, i.e., it would only reduce the immune response against the very antigen comprising the epitope.

Ergo, Dr. Travers declares that one could not equate or extrapolate from the gp120 "suppressor region" to the postulated suppressor epitopes, as Dr. Travers understands the Examiner had endeavored to do in the November 27, 2001 Office Action.

Simply, according to Dr. Travers, if one follows the Examiner's reasoning that suppressor regions and suppressor epitopes are the "same thing", the art did and does not render it possible for the skilled person to identify a T-suppressor epitope and substitute this with a foreign immunodominant T-cell epitope (and also preserve tertiary or secondary and tertiary structure, since the position of such a suppressor epitope may be essential for the structure of the protein).

Hence, Dr. Travers declares that one cannot follow the Examiner's reasoning and arrive at the present invention.

Furthermore, Dr. Travers declares, even though Russell-Jones at page 32 postulates that "[u]sing recombinant DNA technology, the 'suppressor regions' in a number of prospective vaccine proteins including gp120 are removed and replaced," this is not a teaching or suggestion that would or could lead to the instant invention.

Simply, the gp120 suppressor region is not the same as or equivalent to the postulated suppressor epitopes, and one cannot extrapolate from the gp120 suppressor region to the postulated suppressor epitopes.

Moreover, Dr. Travers declares that Russell-Jones at page 32 addresses "vaccine proteins"; that self-proteins are not "vaccine proteins"; that "vaccine proteins" are normally immunogenic; and, that "vaccine proteins" are not normally non-immunogenic. Dr. Travers further declares that there is not normally B-cell autotolerance to "vaccine proteins".

Hence, Dr. Travers asserts that the statement at page 32 of Russell-Jones does not permit extrapolation to self-proteins. In addition, Dr. Travers respectfully submits that the Examiner's positions may be borne out of a failure in the nomenclature in the art and/or a miscommunication between him and Dr. Travers. In any event, it is trusted that his Second Declaration clarifies the nomenclature in the art and any possible miscommunication that may have occurred.

By the Second Declaration, as well as by the Zinkernagel Declaration and Dr. Travers' First Declaration, Applicants have demonstrated that Russell-Jones, either individually or in any combination, fails to teach or suggest the instant invention.

Simply, Applicants have supplied Declarations by Dr. Travers and Dr. Zinkernagel rebutting the positions asserted by the Examiner during prosecution, including in the November 27, 2001 Office Action, and it is respectfully requested that these Declarations indeed be fully and fairly considered as it is earnestly believed that these Declarations clearly and convincingly show that Russell-Jones, either individually or in any combination, fails to teach or suggest the instant invention.

a. ***Dr Travers also asserts that the Examiner's application of Russell-Jones strains the term "immunogen" well beyond its well-known, ordinary, art-accepted definition***

In paragraph 10 of his Second Declaration, Dr. Travers states that he additionally understands that in the November 27, 2001 Office Action, the Examiner relies upon the text at pages 8-9 of Russell-Jones for applying that document as to the present invention. More specifically, the text at pages 8-9 of Russell-Jones states: "The at least one 'immunogen' which forms part of a complex of the invention is any molecule which it is desirable to use to raise an immune response. Typically, the at least one 'immunogen' will be a molecule which is poorly immunogenic, but immunogenic molecules are not excluded." From this, Dr. Travers understand

that the Examiner asserts that a self-protein – a protein that is normally non-immunogenic and as to which there is B-cell autotolerance – can be an "immunogen".

In paragraph 11 of his Second Declaration, Dr. Travers explains that by definition an "immunogen" – whether "immunogenic" or "poorly immunogenic" – elicits an immune response, and there is no B-cell autotolerance thereto; i.e., by definition, a self-protein is not an immunogen. Dr. Travers further explains that if a self-protein is an immunogen, there would not be B-cell autotolerance thereto, and, in essence, the body would be fighting itself – mounting an immunological response against self-proteins.

Dr. Travers states that the plain, ordinary, and art-recognized definition of "immunogen" and the plain, ordinary, and art-recognized reading of Russell-Jones, excludes self-proteins, and is contrary to the Examiner's reading of Russell-Jones and his expansion of the term "immunogen".

Hence, according to Dr. Travers, the Examiner's reading of Russell-Jones and his expansion therein of the term "immunogen" strain the term "immunogen" beyond its ordinary, art-recognized, well-known meaning.

b. ***Dr Travers also explains that the mention in Russell-Jones of luteinizing hormone, somatostatin inhibin and FSH do not allow expansion of the term "immunogen" and unclear assertions of the Examiner are also noted***

In paragraph 12 of his Second Declaration, Dr. Travers states that the mention in Russell-Jones of luteinizing hormone, somatostatin, inhibin and FSH do not allow expansion of the term "immunogen" to include self-proteins, as he understands is attempted by the Examiner in the November 27, 2001 Office Action.

Dr. Travers also understands that the Examiner asserts that: "[t]here is no teaching in Russell-Jones et al. that humans would be immunized with nonhuman modified luteinizing hormone, somatostatin, inhibin or FSH. ... The use of human derived molecules in vaccines for humans was known in the art. ... [V]irtually any self molecule is an immunogen if administered to another species of animal or if administered to the animal from which it was derived wherein it is administered with an appropriate adjuvant. ... Russell-Jones et al. teach that it would be within the skill of a routineer to produce modified fusion proteins wherein Trat was included and wherein the fusion protein still had the activity of the parent molecule."

In paragraph 13 of his Second Declaration, Dr. Travers explains that one could not use an unmodified human self-protein in a human to elicit an immunological response against the self-protein because the self-protien is non-immunogenic; there is normally B-cell autotolerance to the self-protein. Thus, Dr. Travers explains, it is common to use non-human analogs of human self-proteins in humans, to avoid the non-immunogenicity of and B-cell autotolerance to the self-protein. Hence, from the disclosure in Russell-Jones of luteinizing hormone, somatostatin, inhibin and FSH, Dr. Travers opines that one cannot extrapolate that human self-proteins are intended for humans because the same disclosure more than equally indicates to the skilled artisan the use of non-human analogs of human self-proteins in humans. Indeed, Dr. Travers declares that non-human analogs of human self-proteins in humans are consistent with Russell-Jones' use of the term "poorly immunogenic" because non-human analogs of human self-proteins in humans are known to be poorly immunogenic, rather than non-immunogenic (a feature of self-proteins). Thus, in Dr. Travers' view, the skilled artisan, from fully reading Russell-Jones, would not be led to modifying self-proteins. Also, in Dr. Travers' view, the skilled artisan does not view the term "immunogen" as encompassing a self-protein, which is non-immunogenic and to which there B-cell autotolerance, "administered with an appropriate adjuvant." This too strains the art-recognized, well-known, and accepted definition of "immunogen."

In paragraph 14, Dr. Travers states that it is unclear as to what is meant by the Examiner's statement: "Russell-Jones et al. teach that it would be within the skill of a routineer to produce modified fusion proteins wherein Trat was included and wherein the fusion protein still had the activity of the parent molecule." And, Dr. Travers states that it is unclear how this statement pertains to the present invention.

More specifically, Dr. Travers explains that Russell-Jones involves modifying immunogens or antigens – proteins which are normally immunogenic and are not normally non-immunogenic and are not normally B-cell autotolerated – to produce fusion proteins thereof. The "activity of the parent molecule" is eliciting an immune response.

In contrast, the present invention involves modified self-proteins which are normally non-immunogenic and to which there is normally B-cell autotolerance, i.e., "the activity" of the self-protein is not eliciting an immune response.

The modification of the self-protein in the instant invention is so that in comparison to the self-protein, the modified self-protein contains at least one foreign T-cell epitope; the modified self-protein of the instant invention is not a fusion protein. Hence, the modified self-protein does not have the activity of the self-protein, and is not a fusion protein.

Accordingly, to Dr. Travers, the foregoing statements from the November 27, 2001 Office Action, are unclear, especially as to how they may pertain to the instant invention.

Clearly, therefore, Russell-Jones, either individually or in any combination, fails to teach or suggest the instant invention.

Indeed, it is particularly noted that the present claims call for methods for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal; and, from Dr. Travers' reading of Russell-Jones, based upon his education, training and experience in the field to which the present invention pertains, he does not see any teaching or suggestion of such methods, or any teachings, suggestions, motivations, or incentives to modify Russell-Jones to arrive at methods for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal.

Thus, Dr. Travers has rebutted the assertions in the Office Action and has demonstrated that assertions in the Office Action do not seem to make sense with respect to the present invention and that the mention in Russell-Jones of do of luteinizing hormone, somatostatin, inhibin and FSH do not allow expansion of the term "immunogen" to include self-proteins.

Therefore, through the Declarations of Drs. Travers and Zinkernagel, Applicants have amply demonstrated that the instant invention is not taught or suggested by Russell-Jones, either individually or in any combination.

D. ***Russell-Jones, either individually of in any combination, fails to teach or suggest the recitations of the presently claimed invention***

In Section III, *supra*, the recitations of herewith presented claims 56-79 are discussed, and attention is respectfully directed to that Section and to the herewith presented claims, in addition to the following.

The Examiner is respectfully reminded that, "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). *See also Rapport v. Dement*, 59 USPQ2d 1215 (Fed. Cir. 2001) wherein the

Federal Circuit held that the preamble in a method claim (treatment of sleep apneas) was clearly a limitation.

Claims 56-79 provide methods for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein; and, each of the claims specifies that the self- protein is autotolerated by the animal and that there is normally B-cell autotolerance by the animal to the self-protein, as well as whereby, the modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification", it is respectfully submitted, either individually or in any fair combination, fail to teach or suggest the methods of the instant invention.

Note again that Dr. Travers, in his herewith Second Declaration states that the present claims call for methods for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal; and, that from his reading of Russell-Jones, based upon his education, training and experience in the field to which the present invention pertains, he does not see any teaching or suggestion of such methods, or any teachings, suggestions, motivations, or incentives to modify Russell-Jones to arrive at methods for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal.

All of the claims provide that the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein. Claims 57 and 63-67, 69, 70, 71, and 72 recite that the modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein.

Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification", it is respectfully submitted, either individually or in any fair combination, fail to teach or suggest

such a substitution wherein tertiary or secondary and tertiary structure of the self-protein is preserved.

And, in this regard, note again the foregoing discussion of Dr. Travers' Second Declaration (where Dr. Travers finds the Examiner's position to be unclear), and footnote 7, *supra*: The assertion in the Office Action: that "the ability of the immunogen to function as an immunogen is maintained" in Russell-Jones as somehow providing preservation of tertiary structure is inconsistent with the rejections and with the instant invention and inconsistent with the knowledge in the art.[10]

As discussed in Dr. Travers' Second Declaration, and in the foregoing text discussing Dr. Travers' Second Declaration, and in footnotes 7 and 10, if the modified self-proteins maintained the function of the self-proteins, then the modified self-proteins would be non-immunogenic – contrary to the instant invention. Thus, one would not expect immunogenicity from preserving tertiary structure. Furthermore, maintaining immunogenicity, as alleged by the Examiner, is not equivalent to preserving tertiary or secondary and tertiary structure because a single isolated B-cell epitope of an immunogen that has no tertiary structure can have the immunogenicity of the immunogen, without any preservation of tertiary structure (*see* footnote 10 and Dr. Travers' First Declaration at paragraphs 7 and 8). Further, even the art does not equate "function" with "tertiary structure", *cf.* attached abstract of Birken et al. Endocrinology 121(2):657-66 (1987) (Exhibit G) (secondary and tertiary structure maintained, but immunogenicity abolished, showing that one skilled in the art, as attested to by Dr. Travers in his First Declaration, does not equate maintaining immunogenicity with maintaining tertiary structure and *vice versa*).

NOTE ALSO: EXAMPLE 3 MENTIONS A SUBSTITUTION IN TNF-α OF AMINO ACIDS 26-35, A REGION WHERE THE SUBSTITUTIONS DETOXIFY TNF-α. THIS IS FURTHER EVIDENCE THAT THE PRESENT MEANING OF "PRESERVATION OF

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[10] *See also* Dr. Travers' First Declaration of October 6, 2000 at paragraphs 7-8 wherein Dr. Travers explains that the Examiner's argument that preservation of immunogenicity implies preservation of overall tertiary structure is not in line with basic facts in immunology and protein chemistry. For instance, it has been repeatedly demonstrated that short peptides, e.g., of 12 amino acids which do not have any tertiary structure, can be immunogenic, e.g., capable of inducing antibodies cross-reacting with a larger protein of which the peptide is a fragment. Simply, preservation of immunogenicity can be accomplished with a single isolated B-cell epitope from an immunogen, whereas preservation of tertiary structure can involve maintaining a large majority of the B-cell epitopes of the native protein.

TERTIARY STRUCTURE" IS NOT "PRESERVATION OF FUNCTION" AS ALLEGED BY THE EXAMINER.

Thus, the recitations of the claims of preserving tertiary or secondary and tertiary structure, is not taught or suggested by the documents cited in the Office Action.

Claim 58 provides that the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, and said substitution preserving flanking regions comprising at least four amino acids on each side of the peptide fragment, whereas claim 59 calls for flanking regions comprising at least ten amino acids on each side of the peptide fragment, and, claim 60 recites flanking regions comprising at least fifteen amino acids on each side of the peptide fragment. Claims 63-65 call for the flanking regions and preserving secondary and tertiary structure. And flanking regions are also mentioned in claims 70, 71 and 72.

Preservation of flanking regions is not taught or suggested in any of Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification".

Claim 61 provides that "the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein, whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is broken." Claim 66 recites that "the modified self-protein is modified, in comparison to the self-protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving secondary and tertiary structure of the self-protein, whereby the modified self-protein elicits antibodies that are against the self-protein; and, the modified self-protein elicits an immune response in the animal which includes an MHC class II immune response as to the immunodominant T-cell epitope and an autoantibody response in other MHC-haplotypes, and B-cell autotolerance to the self-protein is

broken." Such recitations also appear in claims 70, 71 and 72. These recitations are not taught or suggested in Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification"

Claim 62 provides that the modified self-protein is modified, in comparison to the self-protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, said substitution preserving tertiary structure of the self-protein; and, claim 67 recites that the modified self-protein is modified, in comparison to the self- protein, by being detoxified and by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal, with the substitution preserving secondary and tertiary structure of the self-protein. Such recitations are also found in claims 70, 71 and 72. These recitations are not taught or suggested in Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification".

Claim 68 recites a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

And, claim 69 provides a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, comprising;

preparing different modified self-proteins, wherein:

each modified self-protein is modified, in comparison to the self- protein, by containing a substitution of at least one peptide fragment of the self-protein with a peptide containing at least one immunodominant T-cell epitope which is foreign to the animal,

said substitution preserving secondary and tertiary structure of the self-protein, and

the different modified self-proteins differ from each other with respect to the position of the at least one immunodominant T-cell epitope;

ascertaining which of the different modified self-proteins elicits a desired specific neutralizing effect and thereby ascertaining a desired modified self protein; and

administering to the animal, an immunologically effective amount of the desired modified self-protein, wherein:

the self-protein is normally autotolerated by the animal and there is normally B-cell autotolerance by the animal to the self-protein, and,

the desired modified self-protein elicits antibodies that are against the self-protein, and B-cell autotolerance to the self-protein is broken.

The recitations of these claims are not taught or suggested in Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification".

Claims 70, 71 and 72 recite as subparts a. to n. recitations of claims 56-69 in the alternative. Claim 70 calls for a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein. Claim 71 provides a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, inducing antibody production in the animal against the self-protein of that animal, and eliciting an immune response in the animal which includes an MHC class II immune response as to an immunodominant T-cell epitope which is foreign to the animal and an autoantibody response in

other MHC-haplotypes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein. And claim 72 provides a method for breaking B-cell autotolerance in an animal to a self-protein of that animal, and inducing antibody production in the animal against the self-protein of that animal, earlier and in higher titres, in comparison to the self-protein conjugated to a carrier protein or peptide containing T-cell epitopes, comprising administering to the animal, an immunologically effective amount of at least one modified self-protein, and specifies that the self-protein is normally non-immunogenic in the animal and there is normally B-cell autotolerance by the animal to the self-protein. The recitations of these claims are not taught or suggested in Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification".

Claim 73 calls for a method of claims 56-72 wherein the modified self-protein is a recombinant modified self-protein. Claims 74 and 75 provide methods of claims 56-73 wherein the self-protein is tumor necrosis factor alpha (TNF-α), tumor nucrosis factor beta (TNF-β), gamma interferon (γ-interferon), interleukin 1 (IL-1) or immune globulin (IgE). Claims 76, 78, 79 involves the method of claims 56-73 and 75 wherein the administering includes administering an adjuvant, with claim 77 reciting that the adjuvant comprises calcium phosphate, saponin, quil A or a biodegradable polymer. The recitations of these claims are not taught or suggested in Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification".

Thus, it is clear that Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification", either individually or in any fair combination, fail to teach or suggest the instant invention.

E. *The technical, commercial and financial success of the instant invention is amply demonstrated by the accompanying Schmidt and Borregaard Declarations*

It is quite clear from the foregoing that that Russell-Jones, Hellman, Etlinger "and prior art disclosed in the specification", either individually or in any fair combination, fail to teach or suggest the instant invention, and that no case of anticipation under Section 102 and no case of obviousness under Section 103 has been made by the Examiner.

Nonetheless, Applicants submit herewith the Schmidt and Borregaard Declarations to demonstrate additional indicia of patentability – the technical, commercial and financial success enjoyed by the instant invention.

1. The Schmidt Declaration demonstrates the commercial and financial success of the invention

Submitted herewith is the Declaration of Jakob Schmidt, whose credentials and ability to address issues in this matter are discussed above.

In paragraph 2 of his Declaration, Mr. Schmidt provides a brief history of Phamexa which shows early and continuous commercial and financial success by the present invention, including:

- In **1992**, Pharmexa entered into a **collaborative agreement with Ferring Pharmaceuticals A/S,** spurred by Pharmexa's discovery of the AutoVac™ technology. Also in 1992, the first general proof of principle for the AutoVac™ technology was obtained and the priority application of the present application was filed in 1993.
- **Pharmexa's first private placement of shares** was successfully completed in May **1997**, contributing **net proceeds to the Company of DKK 75 million. Subsequent** thereto Pharmexa obtained **loan financing** from Business Development Finance **totaling DKK 21 million**. Also, in **1997**, Pharmexa entered into a **license agreement** providing **Ferring** the global rights to all human therapeutic indications of the AutoVac™ TNF-alpha pharmaccine. **Ferring pays certain costs** involved with the program which is a subject of the license, and Pharmexa acts as consultants for Ferring during the pre-clinical and clinical development and in the event of future sublicensing.
- **A second private placement** took place in June **1999, providing net proceeds to Pharmexa of DKK 31** million.
- In March **2000**, Pharmexa entered into a **collaboration with Schering-Plough Animal Health (SPAH)** regarding pharmaccines for **veterinary use** based on **Pharmexa's AutoVac™ technology**. On a global, exclusive basis **Schering-Plough received a license** for use of the AutoVac™ technology **in the veterinary field. Schering-Plough pays all research, development, manufacturing and marketing costs. Schering-Plough has paid to Pharmexa a technology transfer fee and will pay up-front and milestone payments** on each product. **Pharmexa will eventually also receive a royalty of Schering-Plough's net profit from product sales.**
- In April **2000, Pharmexa and Ferring announced the approval of the first clinical trial on cancer patients** with the present invention - AutoVac™ technology -

wherein the self-protein is human TNF-alpha **and** later that month **Pharmexa entered into a research and development collaboration with H. Lundbeck** regarding the use of the present invention - AutoVac™ technology as to neurodegenerative diseases. Pursuant to the agreement, **H. Lundbeck pays all expenses related to the program** which is the subject of the license, and **H. Lundbeck paid a down-payment to Pharmexa**. Furthermore, depending on results obtained, **H. Lundbeck can pay Pharmexa as to its license** pertaining to the present invention, **total milestone payments of approximately DKK 150 million** over the entire duration of the project. **Pharmexa will also receive royalties on the sale of final products.** And, **H. Lundbeck also invested DKK 10 million in connection with Pharmexa's IPO on the Copenhagen Stock Exchange** (*see infra).*

- Late **May 2000, Pharmexa was listed on the Copenhagen Stock Exchange, providing DKK 375 million in net proceeds i.e. as previously alluded to, there was an Initial Public Offering (IPO); it raised more than DKK 375 million in net proceeds.**
- In December **2001 Pharmexa announced** an AutoVac™ **cancer license option to Lexigen Pharmaceuticals, Corp.**, a **subsidiary of Merck KGaA** of Darmstadt, Germany, located in Lexington, Massachusetts.
- In April **2002 Pharmexa announced** that **GlaxoSmithKline has an exclusive option on a HER-2 Protein Breast Cancer project**.

In paragraph 3, Mr. Schmidt demonstrates that the commercial and financial successes are due to the instant invention and that patent and technical professionals have favorably evaluated the present invention.

As to the present invention Pharmexa has collaborative partners includeing: Ferring; H. Lundbeck; Schering-Plough; and Lexigen/Merck KgaA.

Pharmexa has raised capital as detailed herein (e.g., private placements, loan, IPO).

From his education, training and experience, Mr. Schmidt states that it is not uncommon, prior to a typical agreement of the nature of those herein mentioned, for there to have been an analysis of the present invention by technical and patent professionals ("due diligence").

Furthermore, from his education, training and experience, Mr. Schmidt states that it is typical for capitalization of the nature discussed herein, for there to have been an analysis by technical and patent professionals ("due diligence") as to technology of Pharmexa, including the

present invention, and especially the present invention, considering that the present invention is a basic, core technology of Pharmexa.

Thus, based on his education, training and experience, Mr. Schmidt states that the agreements Pharmexa has entered into with its partners, as well as the capitalization, have been based on the present invention, including its the unique position in the art as fulfilling an unmet need, and demonstrate commercial and financial success of the present invention.

Indeed, note both direct and indirect revenue herein discussed.

As yet a further indicia of patentability, it is noted that while the USPTO is not bound by decisions of foreign patent offices, nonetheless, foreign patents corresponding to the present application have been granted (*see also* discussion *infra* of Borregaard Declaration), over art as cited against the present application, showing that others skilled in the art and in the patent field have recognized the patentability of the present invention (e.g., Examiners in foreign patent offices). And, on this point, it is noted that in accordance with the foregoing mention of "due diligence", the many entities that have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, demonstrate that others skilled in the art and in the patent field have recognized the patentability of the present invention.

Simply, the many entities have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, as well as the grant of foreign patents, demonstrates that technical and patent professionals must have favorably evaluated the present invention and particularly its position in the art and its patentability.

In his opinion, based on his education, training and experience, including his experience prior to joining Pharmexa and at Pharmexa, Mr. Schmidt states that key to investment decisions made by third parties as to Pharmexa, and to decisions to enter into agreements with Pharmexa as to the present invention, as herein detailed, are the important medical, veterinary and commercial implications of methods for breaking B-cell autotolerance and inducing antibody production against a self-protein by administering a modified self-protein with a peptide containing at least one foreign immunodominant T-cell epitope as recited in the present claims, which was recognized by Mouritsen et al in the present application.

Furthermore, as to the aforementioned due diligence, in Mr. Schmidt's opinion, based on his education, training and experience, including his experience prior to joining Pharmexa and at

Pharmexa, it is respectfully submitted that the due diligence included analysis of the present application, the prior art now cited in the prosecution thereof, the scientific literature, expert opinions and currently available therapies. Based on these analyses, Mr. Schmidt respectfully submits that Pharmexa's partners and investors recognized the potential to develop new treatments for diseases by employing methods for breaking B-cell autotolerance and inducing antibody production against a self-protein by administering a modified self-protein with a peptide containing at least one foreign immunodominant T-cell epitope as recited in the present claims, and as described in the present application.

More specifically, as to the aforementioned due diligence, in Mr. Schmidt's opinion, based on his education, training and experience, including his experience prior to joining Pharmexa and at Pharmexa, it is respectfully submitted that the due diligence included analysis of Russell-Jones, WO 92/05192 and Hellman WO 93/05810 or equivalent documents, and agreements have been entered into with Pharmexa and money was and continues to be invested in Pharmexa, because the inventions described in the present application were and are recognized to be novel and non-obvious in the face of the said prior art, and to meet unmet medical and veterinary needs. In his opinion, based on his education, training and experience, including his experience prior to joining Pharmexa and at Pharmexa, it is respectfully submitted that although many factors influence decisions taken to enter into agreements and make investments as herein detailed, the decision to enter into agreements and invest as described herein was made with significant consideration for the market potential for the technology of the present application and the importance of the present application in establishing a market potential and thus value for the technology. Also, in his opinion, based on his education, training and experience, including his experience prior to joining Pharmexa and at Pharmexa, it is respectfully submitted that the present invention, including methods for breaking B-cell autotolerance and inducing antibody production against a self-protein by administering a modified self-protein with a peptide containing at least one foreign immunodominant T-cell epitope as recited in the present claims, and as described in the present application, is highly valuable, is highly relevant to today's healthcare (medical and veterinary) needs, and thus is highly attractive for investment and funding and licensing and collaboration; and, was not previously taught or suggested.

Thus, as discussed in paragraph 4 of his Declaration, Mr. Schmidt has provided, *inter alia*, clear and convincing evidence of the commercial and financial success and patentability of

the present invention: Clearly, many entities have entered into agreements concerning the instant invention; many have invested in the instant invention; and foreign patent offices have recognized the patentability of the instant invention; *inter alia*. Indeed, it is also noted that many are employed as a result of the instant invention - directly by Pharmexa and indirectly by collaborators who work with respect to embodiments of the instant invention – and, that this further demonstrates investment and proceeds spent as to the present invention, and that this thereby further demonstrates commercial and financial success of the instant invention.

Hence, *inter alia*, clear and convincing evidence of the commercial and financial success and patentability of the present invention has been provided by the Schmidt Declaration.

2. The Borregaard Declaration demonstrates the technical, commercial and financial success of the invention

Submitted herewith is the Declaration of Birger Borregaard, whose credentials and ability to address issues in this matter are discussed above. Documents attached to that Declaration are also listed on the accompanying (in duplicate) PTO-1449; and, the Examiner is respectfully requested to consider and make these documents of record.

In paragraph 2, to demonstrate the technical, commercial and financial success of the instant invention, Mr. Borregaard provides a brief history of Pharmexa, including:

- In 1992, Pharmexa entered into a collaborative agreement with Ferring Pharmaceuticals A/S. The Ferring agreement was spurred by Pharmexa's discovery of the AutoVac™ technology. Thus, Mr. Borregaard reports that the early Ferring agreement was based upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, that it demonstrates commercial success of the present invention. Also Mr. Borregaard reports that in 1992, the first general proof of principle for the AutoVac™ technology was obtained and the priority application of the present application was filed in 1993.
- As to the present invention - AutoVac™ technology - wherein the self-protein is human TNF-alpha (the AutoVac™ TNF-alpha pharmaccine), successful animal results were published in Nature Biotechnology (Dalum et al. Vol 17, p666-669, July 1999), showing technical success and surprising superiority of the instant invention. And, in 1997, Pharmexa entered into a license agreement providing Ferring the global rights to all human therapeutic indications of the AutoVac™ TNF-alpha pharmaccine. Mr. Borregaard reports that this

Ferring agreement was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, demonstrates commercial success of the present invention.

➢ Pharmexa's first private placement of shares was successfully completed in May 1997, contributing net proceeds to the Company of DKK 75 million. Subsequent to the private placement Pharmexa obtained loan financing from Business Development Finance totalling DKK 21 million. Mr. Borregaard reports that this level of financing was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need.

➢ A second private placement took place in June 1999, providing net proceeds to Pharmexa of DKK 31 million. Mr. Borregaard reports that this level of financing was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, this level of financing also demonstrates commercial success of the instant invention.

➢ In March 2000, Pharmexa entered into a collaboration with Schering-Plough Animal Health (SPAH) regarding pharmaccines for veterinary use based on Pharmexa's AutoVac™ technology. On a global, exclusive basis Schering-Plough received a license for use of the AutoVac™ technology in the veterinary field. Mr. Borregaard reports that this SPAH agreement was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need.

➢ In April 2000, Pharmexa and Ferring announced the approval of the first clinical trial on cancer patients with the present invention - AutoVac™ technology - wherein the self-protein is human TNF-alpha and later that month Pharmexa entered into a research and development collaboration with H. Lundbeck regarding the use of the present invention - AutoVac™ technology as to neurodegenerative diseases. Mr. Borregaard reports that the approval of a clinical trial of an embodiment of the present invention indicates technical success of the present invention. Mr. Borregaard reports also that the Lundbeck agreement was based also upon the present invention, including its the unique position in the art as fulfilling an unmet need; and, demonstrates commercial success of the present invention.

➢ Late May 2000, Pharmexa was listed on the Copenhagen Stock Exchange, providing DKK 375 million in net proceeds, leading to a significant expansion of employees

and activities. Thus, there was an Initial Public Offering (IPO) that raised more than DKK 375 million in net proceeds, based on the present invention, including its the unique position in the art as fulfilling an unmet need. Mr. Borregaard reports that this successful IPO demonstrates commercial success of the present invention.

- Mr. Borregaard reports further that during the autumn of 2000, Pharmexa achieved significant results with the present invention in various mouse models: An embodiment of the instant invention wherein the self-protein is HER-2 showed the ability to eliminate HER-2 positive tumors; Professor Paul Foster from Australia using an embodiment of the instant invention wherein the self-protein is IL-5 showed a complete remission of asthma in asthmatic mice; and Professor Tanaka at University of Tokyo using an embodiment of the instant invention wherein the self-protein is RANKL confirmed significant reduction in bone loss in several models of osteoporosis. According to Mr. Borregaard, these results further illustrate the technical success and surprising superiority of the present invention.

In paragraphs 3 and 4 of his Declaration, Mr. Borregaard details Pharmexa's numerous collaborative partners as demonstrating the commercial success of the instant invention. Pharmexa's collaborative partners as to the present invention include: Ferring; H. Lundbeck; Schering-Plough; and Lexigen/Merck KgaA. According to Mr. Borregaard, the agreements entered into with these and other partners is based on the present invention, including its the unique position in the art as fulfilling an unmet need, and demonstrate commercial success of the present invention.

In paragraph 5 of his Declaration, Mr. Borregaard provides literature demonstrating success and art recognition of the instant invention.

In paragraph 6 of his Declaration, Mr. Borregaard discusses Pharmexa' numerous programs, results, partners and collaborations as demonstrating the success and art recognition of the instant invention.

For instance, programs in various stages involving embodiments of the instant invention include:

Indication	Name	Target	Status	Partner
Breast cancer	ME103	HER-2 DNA	Phase I/II	
Breast cancer	ME104	HER-2 Protein	Late Pre-Clinical	
Asthma	ME105	IL5	Pre-clinical	
Osteoporosis	ME107	RANKL	Research	
Allergy	ME108	IgE	Research	
Neurodegenerative disorder	ME106	Not Disclosed	Research	Lundbeck
Veterinary conditions		Not Disclosed	Target Species	Schering-Plough
Cancer		Not Disclosed	Research	Lexigen/Merck KGaA

These programs, results, and collaborations demonstrate success and art-recognition of the instant invention.

In paragraph 7, Mr. Borregaard mentions that foreign patents corresponding to the instant application have been granted, and that technical and patent professional must have favorably evaluated the instant invention. The issuance of foreign patents shows that others skilled in the art and in the patent field have recognized the patentability of the present invention (e.g., Examiners in foreign patent offices). And, on this point, it is noted that it is not uncommon for an entity to study both a technology and the patentability of the technology before entering into an agreement with respect thereto – this is commonly called "due diligence" and can involve technical and patent professionals. It is likewise not uncommon for an entity or an individual to reseach a company's technology and the patentability thereof before investing in the company – also called "due diligence" and can involve technical and patent professionals.

Mr. Borregaard reports that the many entities have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, demonstrate that others skilled in the art and in the patent field have recognized the patentability of the present invention.

Simply, the many entities have entered into agreements concerning the instant invention and the many that have invested in Pharmexa and hence the instant invention, as well as the grant of foreign patents, demonstrates that technical and patent professionals must have favorably evaluated the present invention and particularly its position in the art and its patentability.

Hence, as discussed in paragraph 8 of Mr. Borregaard's Declaration, clear and convincing evidence of the commercial success, technical success, and art recognition, and patentability of the instant invention has been provided. Clearly, many entities have entered into

agreements concerning the instant invention; many have invested in the instant invention; many successful results of embodiments of the instant invention have been reported; clinical and pre-clinical trials of embodiments of the instant invention are underway; and foreign patent offices have recognized the patentability of the instant invention; *inter alia*. Indeed, it is also noted that the many employed as a result of the instant invention - directly by Pharmexa and indirectly by collaborators who work with respect to embodiments of the instant invention – further demonstrate investment and proceeds spent as to the present invention and thereby further demonstrate commercial success.

Therefore, it is respectfully submitted that by the Schmidt and Borregaard Declarations, Applicants have provided, *inter alia*, clear and convincing evidence of the commercial success, technical success, art recognition and patentability of the present invention.

F. ***The rejections under Sections 102(b) and 103 are overcome - reconsideration and withdrawal of these rejections are requested***

Accordingly, in view of the amendments, remarks and attachments herewith, including the accompanying Declarations, as well as in view of the previously-submitted First Declaration of Dr. Travers (the October 6, 2000 Declaration of Dr. Travers), and the arguments and remarks of record, the rejections under Sections 102(b) and 103 are addressed and overcome. Reconsideration and withdrawal of the rejections under Sections 102(b) and 103 are respectfully requested.

G. ***The rejections under Section 112 are overcome - reconsideration and withdrawal of these rejections are requested***

As discussed above, claims 54 and 55 were rejected under Section 112, first paragraph as allegedly containing subject matter not described in the specification. And, claims 26, 28, 45-47 and 53-55 were rejected under Section 112, second paragraph as being allegedly indefinite for failing to particularly point out and distinctly claim. Also, it was above-noted that the Office Action seems to not have considered the October 6, 2000 Declaration of Dr. Paul J. Travers, as well the disclosure in the present application on these issues; and, it is respectfully requested that Dr. Travers' First Declaration and the disclosure in the present application be fully and fairly considered.

More in particular, claims 54 and 55 were rejected under Section 112 based on the phrase "to introduce minimal tertiary structure changes in the unmodified self-protein, and claims 26,

28, 45-47 and 53 were rejected because of the phrase "essentially preserve the overall tertiary structure." These recitations do not appear in the instant claims; and therefore, the Section 112 rejections are moot and overcome.

Nonetheless, with respect to the "preserving" recitation in the instant claims and the recitation of the previous claims, attention is respectfully directed to paragraphs 4-8 of Dr. Travers' First Declaration and the arguments and remarks of record, and the documents attached hereto and the comments herein.

In sum, Dr. Travers has pointed to numerous portions of the application to support the "preserving" recitations and indicates that preservation of tertiary structure requires that a large majority of B-cell epitopes in the native self-protein exist in the modified self-protein.

Rules that an immunologist or protein chemist of ordinary skill in the art would follow at the effective filing date, without any undue experimentation, to meet the "preserving" recitations in the instant claims and the similar recitation in the previous claims include: making substitutions in regions that do not contribute to tertiary or secondary and tertiary structure, e.g., regions that cannot be resolved by X-ray crystallography, typically flexible loops or flexible termini; substituting regions having a particular secondary structure with a peptide having a similar secondary structure, e.g., alpha-helix substituted with an alpha-helix as in Example 3 of the present application (amphiphatic alpha helix), or beta sheet substituted with a beta sheet; preserving disulphide bridges and avoiding introduction of new disulphide bridges when making substitutions; avoiding changing overall hydrophilicity and charge of the substituted region; avoiding introduction and deletion of proline residues; and avoiding dramatic changes in the overall length of the polypeptide.

Thus, the skilled artisan can easily preserve tertiary or secondary and tertiary structure.

Furthermore, as discussed above, the meaning of the term "preservation of overall tertiary structure" and the "preserving" recitations in the instant claims, is clearly not a requirement that the modified self-protein must be functionally equivalent to the naturally occurring self-protein. And, since the specification teaches that it is advantageous to preserve a maximum number of B-cell epitopes compared to the original self-protein, it must be concluded by the skilled person that this is the true meaning of the "preserving" recitations of the instant claims and the "preservation of overall tertiary structure" recitation of the previous claims. NOTE AGAIN: EXAMPLE 3 MENTIONS A SUBSTITUTION IN TNF-α OF AMINO ACIDS 26-35, A

REGION WHERE THE SUBSTITUTIONS DETOXIFY TNF-α. THIS IS FURTHER EVIDENCE THAT THE PRESENT MEANING OF "PRESERVATION OF TERTIARY STRUCTURE" IS NOT "PRESERVATION OF FUNCTION" AS ALLEGED BY THE EXAMINER.

It is very simple to determine whether or not most or all B-cell epitopes of a protein are preserved in a variant protein. For instance, the variant can be used in the preparation of a polyclonal antiserum in a heterologous host. After that, a competitive immune assay can be used to determine whether or not the variant and the native proteins are capable of competing for binding to the polyclonal antiserum. If this is the case, the B-cell epitopes are preserved (both the segmental and the assembled topographic epitopes). Competitive immunoassays have been used for such purposes for many years (normally to detect differences), *cf.* the attached Abstracts of Crabb et al. J Biol Chem 266(25):16674-83 (1991) and Gerity & Conway J Immunol Methods 68(1-2):131-5 (1984) (Exhibits H and I).

Further, if monoclonal antibodies are prepared against the self-protein, some of these will recognize assembled topographic epitopes. Such antibodies will only bind a variant protein that has the same assembled topography - this is an excellent indication that tertiary structure is preserved.

And, physical methods for determining secondary and tertiary structure were also readily available at the effective filing date, e.g.: Circular dichroism (*cf.* Exhibit J: Abstract of Fabian et al. Biochem Biophys Res Commun 191(1): 232-9 (Feb. 26, 1993)), FTIR spectroscopy (*cf.* Exhibit K: Abstract of Lamba et al. Biochim Biophys Acta 1163(2):113-23 (May 13, 1993)), NMR (*cf.* Exhibit L: Abstract of Klaus & Schomburg J Mol Biol 229(3):695-706 (Feb. 5, 1993)).

Tertiary structure could be predicted as of the effective filing date of the instant invention because at that time the concept of homologous proteins existed ("highly homologous proteins" are those that resemble each other very much in tertiary and/or quaternary structure).

But, more importantly, the art had provided methods for determining the tertiary structure of a protein, *cf.* WO 91/16683 (copy attached as Exhibit M); *see also* corresponding U.S. Patent No. 5,265,030.

Therefore, the "preserving" recitations in the instant claims is indeed clear and definite; and the "essentially preserve overall teritary structure" and like recitations of the previous claims were also clear and definite. Moreover, these recitations are disclosed in the instant application

and one skilled in the art can practice these recitations, without any undue experimentation. Accordingly, the present application contains a written description of and enablement for the "preserving" recitations in the instant claims and the "essentially preserve overall teritary structure" and like recitations of the previous claims, especially when these recitations are fully and fairly considered in view of the knowledge in the art.

Thus, the Section 112 rejections are overcome; and, it is respectfully requested that the Section 112 rejections be reconsidered and withdrawn.

CONCLUSION

In view of the amendments, remarks, and attachments herewith, including the Declarations herewith, and the arguments, remarks, and submissions of record, including the articles and the Travers Declaration previously submitted, the application is in condition for allowance. Favorable reconsideration of the application, reconsideration and withdrawal of the rejections, and prompt issuance of a Notice of Allowance, or an interview with a view towards reaching agreement on allowance, are earnestly solicited.

Respectfully submitted,

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